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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,178	02/15/2002	Chang-Zheng Chen	0399.2027-001	9519

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,178	CHEN ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/15/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0103*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16 are pending in the application.

Claim Objections

Applicant is advised that should claims 3, 9 and 10 be found allowable, claims 5, 11 and 14 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 12 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. A claim that depends on itself does not further limit the claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 9 and 11 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In the instant case, the claims recite "two different functionally important genomic loci of hematopoietic stem cells" for which the reporter DNA is targeted. This class of "functionally important genomic loci of HSC" encompasses potentially a large number of genomic loci, including any promoters or functional genes, that are necessary for HSC function. The specification only discloses four genes (SCL, Ikaros, LMO2 and LYM1) that may be used for the claimed method. However, the specification fails to disclose the structure and functional relationship for the class of genomic loci that are used in this method. In other words, the specification fails to teach the structure or the functional property that these genomic loci must share for use in this claimed method. Therefore, the

specification fails to describe a representative number of species by their complete structure, nor other identifying characteristics. Thus, the written description requirement is not met.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention

The nature of the invention is a method for identifying hematopoietic stem cells comprising targeting two different reporter construct into two different functionally important genomic loci of hematopoietic stem cell (HSC), so that the reporter is driven by the promoter of the genomic locus, thereby producing a population comprising successfully targeted hematopoietic stem cells and other cells; and subjecting said cell population to conditions under which successfully targeted HSC survive and the other cells in the population do not survive,

thereby identifying HSC. The claims are further drawn to isolated HSC that are produced by said method.

The breadth of the claims

The breadth of the claims is very broad. In the instant case, the broadest claim encompasses a method of identifying HSC by targeting any two reporter genes to any functionally important genomic loci of said HSC, and selecting for cells express both markers. The method also encompasses the identification of HSC from any source or species.

Amount of guidance in the specification and Working Examples

The teaching of the specification is very limited. The specification only discloses four genomic loci including SCL, Ikaros, LMO2, and LYL1 that can be targeted for identifying HSC. Furthermore, the specification only discloses one method for targeting the reporter DNA to the specific loci, such method involves the generation BAC with reporter DNA by homologous recombination, and subsequent generation of transgenic mouse carrying said BAC-reporter construct in its genome. However, the specification fails to teach whether the cells express both marker genes display the characteristic of HSC. Furthermore, the specification fails to teach how to identify HSC from other species, especially human HSC since one cannot generate a transgenic human for this purpose. Moreover, the specification does not disclose how to identify HSC from an isolated population of cells, for example, cord blood, peripheral blood or bone marrow. As such, one skilled in the art would have to rely on the teaching of the prior art to practice the claimed invention.

The state of art and the level of predictability in the art

The state of art at the time of filing defines a HSC as a cell isolated from the blood or bone marrow that can renew itself, can differentiate to a variety of specialized cell, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death (see page 43, NIH report 2001: Stem Cells). Although much research has been focused in this area, there is no single phenotypic characteristic that can be used to define uniquely human or murine HSC currently (see page 43-44 NIH report, and page 4, Uher et al, 2003). The NIH report further indicated that the HSC has an identity problem because its rarity (1 in every 10,000 to 15,000 in bone marrow, 1 in 100,000 in peripheral blood cell), multiple type and phenotypic indistinguishable from other blood or bone marrow cells. At present, isolation of HSC is mainly based on using multiple cell surface marker including CD34, CD133, and CD90, and lack of expression of a series of other antigens that mark differentiation lineages. For example, one widely used criterion is the absence of CD38 on cells that express CD34. Other phenotypic characteristics, such as low level staining by the activation sensitive probe rhodamine 123 or the active efflux of both rhodamine 123 and Hoechst 33342 dyes, have also been used to define a primitive subset of bone marrow cells (page 4, 2st paragraph of Uher et al.).

The inability to purify stem cells to a homogenous population makes the use of functional HSC assays necessary. To this date, the "gold standard" for proving that a cell is indeed an HSC is by injecting the cell into a lethally irradiated mouse, and observing whether the mouse survives and develop all types of blood cells that bear a genetic marker of the donor cell. The most definitive measure of mouse LTRC is their ability to compete for engraftment against other HSC (see page 4, 2nd paragraph of Uher et al., and page 15 Uher et al., bottom). Since *in vivo*

repopulation experiments cannot be done in humans, surrogate assays and xenogeneic transplant models have been developed to enumerate human HSC (see page 5, 1st paragraph of Uher et al).

Another obstacle in the HSC research is the difficulty in grow or maintain true HSCs in culture (see page 49, NIH report). Uher et al. also point out that although *in vivo* data indicate that HSC can undergo a moderate to large number of fully self-renewing divisions wherein the actual number of HSC can increase, it has been impossible to reproduce this in an *in vitro* setting. Despite of a plethora of culture systems, growth factors and stroma cell lines, the best results reported to date only lead to maintenance of stem cell activity for limited times and/or to very modest increases in cell numbers. Uher et al. conclude that it is surprisingly difficult to manipulate HSC without losing them as a result of differentiation or apoptosis, and the combination that will allow HSC to be manipulated in a therapeutic setting remains unknown.

The prior art is silent on a method of identifying HSC based on the co-expression of functionally important genomic loci such as SCL and Ikaros. There are many functionally important genes that are involved in the proliferation or differentiation signaling of HSC identified to date, however, their expression is not limited to the HSC only. For example, transcription factors related to lymphoid lineage commitment such as Ikaros, PU.1 and GATA3 gene transcription are also detected in cells which give rise to non-lymphoid progeny (see page Geogopoulos, 224, 2nd col., 3rd paragraph, lines 12-18). As such, the nexus between expression of two functionally important genomic loci and the cell being a true HSC is missing. Whether a cell express two marker protein at two important genomic loci of HSC is an HSC is unpredictable.

Furthermore, the specification only teaches a method for targeting the reporter DNA to the specific loci, such method involves the generation BAC with reporter DNA by homologous recombination, and subsequent generation of transgenic mouse carrying said BAC-reporter construct in its genome. Such method cannot be adopted to human cells because one cannot generated transgenic human for this purpose. Uher et al. indicates that HSC have stubbornly resisted most manipulation thus far, and it might be a while longer before culturing of HSC is a routine as that of embryonic stem cells today. Consequently, in a mixed population of cells, such as cord blood, peripheral blood cells, whether targeted introduction of reporter DNA to the stem cell important genomic loci can be achieved in HSC by homologous recombination is unpredictable.

Lastly, the claims recite the step of subjecting the population of cells to conditions under which successfully targeted HSCs survive and the other cells in the population do not survive. As such, the reporter DNA must be a gene encoding a protein that has selection advantage under certain condition. Thus, not all reporter DNA can be used for this purpose. For example, β-gal, luciferase, or GFP cannot be used for this purpose. Therefore, the claimed method is not enabled for using any type of reporter DNA.

In view of the art recognized unpredictability in manipulating and identifying a true HSC, the specification fails to teach a method that can overcome such difficulties. Consequently, one skilled in the art would have to engage in undue experimentation to practice the method as claimed. Therefore, the claimed invention is not enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-11, the term "targeting" or "targeted" renders the claims indefinite because it is unclear what this term encompasses in the contexts of reporter DNA and HSC. In other words, it is unclear how the reporter DNA is targeted to the cell, and how to determine an HSC is "successfully targeted." Applicants are suggested to use words such as "introducing" or "incorporated into the genome" which describes the method steps more clearly. In addition, it is unclear how HSCs are selectively targeted in step a) of the claimed method. The claim only recites targeting the HSCs in step a), whereas step b) recites a population of the cell comprising HSCs as well as other types of cell.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER